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The relationship between negative symptoms and depression in schizophrenia – A systematic review

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Abstract

Objective: Provide an update on the evidence base for the nature of the relationship between negative symptoms and depressive features in people with schizophrenia, and propose new models that reflect their complex relationship.

Method: A systematic review following PRISMA guidelines. 2210 articles were identified from EMBASE, PsychInfo and Medline and a further 2 articles were hand searched from references. 27 met inclusion criteria and were included in the review.

Results: In schizophrenia, primary evidence suggests symptoms of low mood, suicidal ideation and pessimism have more specificity for depression whereas alogia and blunted affect may have more specificity as negative symptoms. Anhedonia, anergia and avolition may be common to both.

Conclusion: It may be possible to further distinguish depressive features from negative symptoms in schizophrenia when detailed phenomenology is considered. However, in a proposed dimensional model, these two domains continue to share certain phenomena, highlighting their close relationship.

Key words: Depression, schizophrenia

Summations

- Symptoms such as low mood, suicidal ideation and pessimism are cited within a depressive domain, whereas symptoms such as alogia and blunted affect appear to indicate negative symptoms. Anhedonia, anergia and avolition occur across both domains.
- Detailed understanding of underlying phenomenology may provide potential treatment targets as well informing future research assessing underlying aetiological mechanisms.

Considerations

- Research methodologies of included studies were highly variable, leaving interpretation of the results open to bias.
- Future studies should focus on employing appropriate scales to assess depression, and consider the negative symptoms as two dissociable sub-domains (avolition-apathy and expressive-deficit).

Introduction

Schizophrenia has been conceptualised as a neuro-developmentally mediated, cognitive illness marked by a more unfavourable outcome than affective disorders (1). Positive and negative symptoms and cognitive dysfunction are core features of the illness, however there is a phenomenological overlap between schizophrenia and mood disorders (2); mood symptoms are common features in prodromal psychosis and established schizophrenia (3), while psychotic symptoms frequently occur with severe mood disorders. Such observations, as well as burgeoning biological evidence (4, 5), challenge the Kraepelinian dichotomy. One area of perhaps neglected phenomenological enquiry is negative symptoms; negative symptoms may present variously as a loss of motivation to act and a lack of the elements that make up the normal repertoire of social and emotional responsiveness (6), yet these are also commonly seen in depression (7).

Andreasen (8) characterised negative symptoms as consisting of affective blunting or flattening, alogia, anhedonia/asociality and avolition/apathy and attention; although attentional deficits may indicate cognitive impairment rather than a manifestation of a negative symptoms. Much of the earlier research exploring negative symptoms has assumed that they form one discrete syndrome. However, factor analyses have isolated two sub-domains within negative symptoms (9, 10) namely avolition-amotivation and expressive deficits. The avolition-amotivation sub-domain is considered to be formed of the symptoms; avolition, asociality and anhedonia, whereas the diminished expression sub-domain comprises blunted affect and alogia (11-13).

Depression is a mood disorder that is characterised by low mood and anhedonia (14). Affective symptoms have been recognised as occurring commonly in non-affective psychosis, in 50%- 80% of patients at some point during their illness (15,

16). Previously, Siris et al. (17) found that half of individuals with post-psychotic depression also met criteria for negative symptoms, implying a syndromal overlap between depressive and negative symptoms. However Addington et al. (18) designed the Calgary Depression Scale for Schizophrenia to assess depression separately from negative symptoms and also from positive symptoms and extrapyramidal symptoms such as parkinsonism.

Previous models have conceptualised depression and negative symptoms as belonging to distinct and separate clinical syndromes (19-23). Within a dimensional approach to psychoses, a model of overlapping domains with distinct presentations allows further exploration of the heterogeneity involved. Initially presented as three domains of reality distortion, psychomotor poverty and disorganization syndrome (24), more recently mood symptoms have been included in five factor models; positive symptoms, negative symptoms, depression, mania and cognitive (25). These models of symptoms of psychoses allow for co-morbidity in more than one domain, with an individual patient presenting with varying degrees of symptom severity in each domain.

The exact nature of the relationship between depression and negative symptoms in a 'non-affective' psychotic illness such as schizophrenia remains uncertain. Identifying depression in schizophrenia and treating this symptom domain is essential given that depression in schizophrenia has been associated with poor prognosis and suicide (3, 26). Understanding this heterogeneity further is potentially important for the elucidation of the underlying aetiological mechanisms and the development of better, targeted, treatments.

Aim of the study

The aim of this systematic review was to provide a novel and up-to-date review of the evidence for the phenomenological co-occurrence of depression and negative symptoms in schizophrenia.

Method

A systematic search and review following the PRISMA guidelines (27) was conducted. We limited our search to studies examining depression and negative symptoms in schizophrenia and excluded studies looking at other conditions. There were no limits put on the origin or date of a publication.

Inclusion criteria

1. Studies that aimed to report the relationship between negative and depressive symptoms in schizophrenia.
2. Studies that were published in English.

Exclusion criteria

1. Review articles, letters to editors and presentation abstracts
2. Papers that reported depression and only other (non-negative) symptom domains (e.g. positive symptoms and depression; social functioning, insight)

The following databases were searched on 05/01/2018: MEDLINE, PSYCHINFO, and EMBASE. The following search terms were used: “SCHIZOPHRENIA”; or

"SCHIZOPHRENIA, CATACTONIC" or "SCHIZOPHRENIA CHILDHOOD" or "SCHIZOPHRENIA, DISORGANISED" or "SCHIZOPHRENIA, PARANOID" or "PSYCHOTIC DISORDERS" or "SCHIZOPHREN*" or "PSYCHOSIS" or "PSYCHOSES" or "FIRST EPISODE PSYCHOSIS" and "DEPRESSION" or "DEPRESSIVE DISORDER" or "DYSTHYMIC DISORDER" or "DEPRESSIVE DISORDER, MAJOR" or "TREATMENT RESISTANT" or "DEPRESSION" or "AFFECTIVE DISORDER" or "MOOD DISORDERS" and "NEGATIVE SYMPTOM" or "ANHEDONIA" or "APATHY" or "ALOGIA" or "ASOCIALITY" or "AFFECTIVE FLATTENING" or "BLUNTED AFFECT" or "AVOLITION" or "SOCIAL WITHDRAWAL" or "LOSS MOTIVAT*" or "LACK MOTIVAT*" (see supplementary table 1 for the full search strategy)

Two reviewers (CRK and RU) independently reviewed all the papers screened and agreed on which papers should be included in the review (see Table 1).

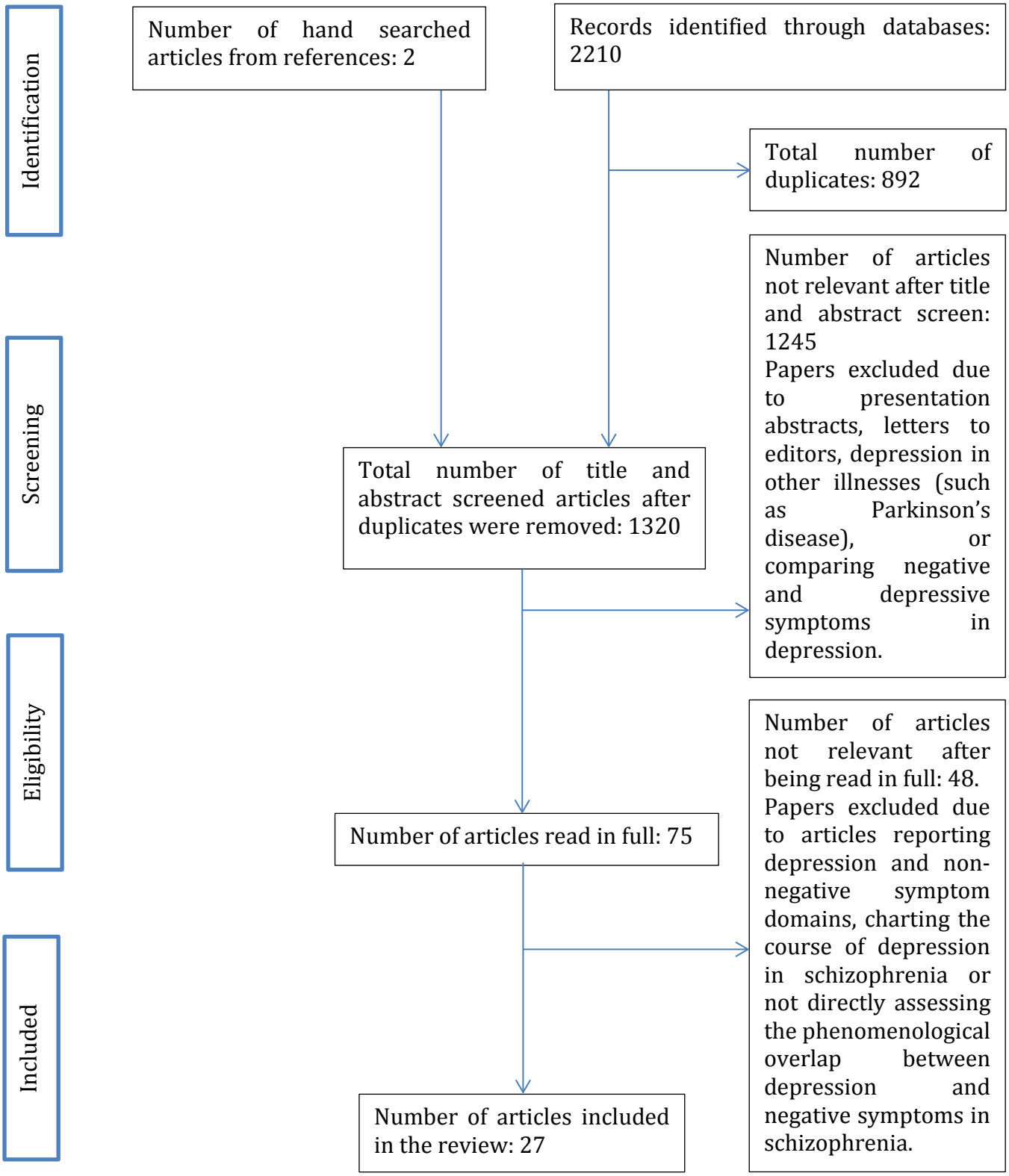

Figure 1 : Flow diagram of studies included in the systematic review

Author	Year	Number of participants (Inc. gender)	Population	Depression scale	Negative symptoms scale	Antidepressant usage	Conclusions	Other information
Whiteford et al. (28)	1987	40 male patients with chronic schizophrenia	Outpatients	HRSD,	SANS	Unknown	Nx and Dx overlap on loss of energy, drive and interest and anhedonia/asociality, but can be differentiated on features such as poverty of thought and speech, and poor attention/concentration, which were related to Nx but not Dx.	Cross-sectional
Barnes et al. (29)	1989	194 chronic schizophrenia	Inpatients	BDI	SANS (specific rating for Anhedonia).	Unknown	Confirmed a Dx syndrome which was distinct from Nx symptoms and was not a result of pharmacotherapy.	Cross-sectional
Pogue-Geile (30)	1989	44 (40 with schizophrenia and 4 schizoaffective)	Outpatient	SADS-L; BDI,	SANS	Unknown	There was no significant difference between Nx and Dx in schizophrenia.	Cross-sectional
Kulhara et al. (31)	1989	95 patients with schizophrenia	Patients were referred.	BPRS	BPRS (total score); SANS; SAPS	Unknown	Retardation, lack of energy and slowness were associated with Nx. Depressed mood was associated with Dx.	Cross-sectional
Ragin et al. (32)	1989	25 (12 schizophrenia, 13 depressed	Inpatient, and then	SADS	TLC	Unknown	During inpatient admission, Dx patients experienced more poverty of speech than	Longitudinal

		patients)	followed up after discharge				SCZ patients. At follow up, poverty of speech increased in SCZ patients but stayed the same in Dx patients.	
Newcomer et al. (33)	1990	69 schizophrenia (all male)	Unmedicated inpatients	BPRS:DEP (depressed mood, guilt, anxiety and somatic concern); HRSD	BPRS:NEG (blunted affect, emotional withdrawal, motor retardation).	All unmedicated	High association between Nx measures and Dx measures. Other items reflecting other aspects of Dx did correlate with the Nx measures.	Retrospectively drawn sample
Koreen et al. (16)	1993	70 patients with schizophrenia/ schizoaffective (39 male, 31 female).	Inpatients	Extracted scores on the HDRS	SADS; SANS; CGI-S	Following baseline assessment, patients prescribed antidepressants and antipsychotics	Dx are present and prevalent in the first episode and occur concurrently with psychotic symptoms and resolves as the psychotic episode remits. Dx is a core feature of schizophrenia and correlates with Nx and Px.	Prospective
Kibel et al. (34)	1993	73 schizophrenia (51 male, 22 female)	Inpatients	Montgomery - Asberg Depression rating scale	SANS; NSRS; PANSS (total), Manchester scale, Montgomery	Unknown	Subjective sadness, pessimism and suicidal intent belong to the Dx. Observed sadness, lassitude and inability to feel were more strongly associated with Nx.	Cross-sectional

					Schizophrenia Scale.			
Tharyan et al. (35)	1994	46 patients with schizophrenia	Unknown	HDRS	SANS	Initially unmedicated and then medicated	Depressed patients showed fewer negative symptoms than non-depressed.	Longitudinal
Sax et al. (36)	1996	17 with schizophrenia (including schizophreniform and psychosis not specified), 25 with depression	Inpatient	HRSD	SANS; SAPS	Unknown	Dx and Nx correlated on poor motivation, social withdrawal and anhedonia, which were not attributable to any drug effects.	Cross sectional
Nakaya et al. (37)	1997	89 with schizophrenia/ schizophreniform (39 male, 47 female	Inpatients	HRSD (17 item); PANSS depression item	PANSS (total negative symptom subscale)	Unknown	There was a lack of association between improvement of Dx and Nx.	Prospective and longitudinal
Nakaya et al. (38)	1998	86 patients with schizophrenia or schizophreniform. (39 male, 47 female).	Inpatients	HRSD (17 item version)	PANSS (total negative symptom subscale)	Unknown	Differences in the composition of the Dx syndrome were observed in the acute and chronic phase of schizophrenia. Dx unrelated to Px and Nx.	Prospective and longitudinal
Zisook et	1999	60 patients	Outpatie	HDRS and	SANS and	Medicated	Severity of Dx did not	Cross-

al. (39)		with schizophrenia, 60 healthy controls	nts	BPRS	BPRS		correlated with severity of Nx.	sectional
Baynes et al. (40)	2000	120 with chronic schizophrenia (78 male, 42 female)	out-patients	BDI; HDRS; CGISS; BPRS (anxiety/depression items)	SANS	No antidepressants	No association between Dx and Nx in schizophrenia. Dx are more common in the active illness.	Cross-sectional
Romney et al. (22)	2001	54 schizophrenia 27 MDD (55 male 26 female)	36 in-patients; 45 out-patients	BDI; HRSD; MDI;	PANSS (total negative subscale score); PAS; SAS; Maine scale	MDD patients took antidepressants	Anhedonia is more closely aligned with Dx.	Cross-sectional - Factor analysis
Tapp et al. (41)	2001	104 with schizophrenia and depression	Inpatients	HRSD	SANS; BPRS (total negative subscale)	Unknown	Dx are prevalent during acute psychosis and are reduced following treatment with antipsychotic medication.	Experimental – double blind trial.
Muller et al. (42)	2002	57 (53 schizophrenia, 4 schizoaffective) 36 Male 21 female	Inpatients	CDSS	PANSS (total negative subscale)	14% patients received antidepressants	Dx is heterogeneous and occurs in schizophrenia. These symptoms are separate from emotional blunting and emotional blunting is independent from Dx. Affective blunting was observed in patients with	Cross-sectional

							residual and disorganised schizophrenia.	
Oosthuizen et al. (43)	2002	80 (41 male, 39 female)schizophrenia/schizophreniform	Unknown	PANSS - D	PANSS (total negative subscale)	Antidepressants were used	Dx were common in the first episode and were also independent from Nx.	Experimental – open labelled trial.
Bottlender et al. (44)	2003	76 (33 schizophrenia, 43 depression)	Inpatient	Montgomery-Asberg Depression Rating scale	SANS	Unknown	For Dx patients, Nx emerged for within 3 months prior to hospitalisation. In patients with SCZ, Nx were present for 12 months prior to admission and were more enduring than in those with Dx. Also, Nx in Dx patients was associated with Dx symptoms but not in SCZ patients.	Cross sectional and longitudinal
Maggini et al. (45)	2004	128 chronic with schizophrenia (87 male, 41 female)	Unknown	CDSS	SANS; SAPS; SENS	Unknown	Dx patients with schizophrenia showed higher scores for Px, anhedonia, asociality, cognitive overload, basic 2012emotional impairment and heightened awareness of functional deficits. Dx did not correlate with Nx.	Cross-sectional
Hafner et al. (46)	2005	130 first admission patients with	first admission	Retrospective Assessmen	IRAOS	81% of schizophrenia	Dx and Nx are prominent in the prodromal stages of Dx and schizophrenia and	Cross-sectional

		schizophrenia. 130 with depression. 130 healthy controls	patients	t of the Onset of Schizophrenia		patients and 79% of depressed were drug naïve.	transition to psychosis or depression later in the illness.	
Hafner et al. (47)	2005	130 with schizophrenia (51%male, 49% female), 130 depressed (51%male, 49% female) and 130 controls (51%male, 49% female)	Patients from Mental health institution	IRAOS	IRAOS	Most were medication naïve (both antipsychotic and antidepressants)	Dx and schizophrenia begin with combined symptomology consisting of Dx and increasing impairment.	Cross-sectional
Rocca et al. (48)	2005	78 (46 males and 32 females) with schizophrenia	Outpatient	CDSS	PANSS (total negative subscale)	Unknown	Nx were separate from those of Dx. Also, outcome for patients with Dx and Nx was less favourable. Dx and Nx did not share the same pattern of clinical and cognitive predictors.	Cross-sectional
Upthegrove et al. (15)	2010	92 with FEP (87% - non-affective psychosis, 13% - affective psychosis.	EIS	Prodromal depression: SCAN; Baseline and follow up	PANSS (total negative subscale)	Unknown	Dx occurs, waxes and wanes throughout early psychosis and predicts illness with prodromal Dx predicting Dx in the early course and future Dx episodes throughout the	Prospective study

				depression: CDSS			course of illness.	
Majadas et al. (49)	2012	90 (59% male, 41% female - 73 with schizophrenia, 2 schizophreniform and 15 with schizoaffective disorder)	Outpatient clinic	CDSS	PANSS (total negative subscale); SANS; SUMD	Patients with a diagnosis of depression or treated with antidepressants were excluded.	Dx is frequent in the stable phase of schizophrenia and is associated with greater severity of illness. Dx is indicative of greater severity of the illness. Dx and Nx are poorly associated.	Cross-sectional
Chiappelli et al. (50)	2014	98 with schizophrenia (67% male, 33% female) and 117 control (43% male, 57% female)	Local community mental health clinics.	Maryland Trait and State Depression - scale	BNSS	36 were taking antidepressants, 15 were taking mood stabilisers	State and trait aspects of Dx and Nx can be separated in schizophrenia. In the schizophrenia sample, Nx and Dx did not correlate.	Cross-sectional - Factor analysis
Rossi et al. (51)	2017	921 schizophrenia	outpatients	CDSS	BNSS	Unknown	High negative symptoms predict depression	Cross-sectional

Beck Depression Inventory (BDI); Hamilton Depression Rating Scale (HDRS); Clinical Global Impression Severity Scale (CGI-S); Scale for the Assessment of Negative Symptoms (SANS); Extrapyramidal Rating Scale (EPRS); Brief Psychiatric Rating Scale (BPRS); Barnes Akathisia Rating Scale (BARS); Significant Others Scale (SOS); Brief Negative Symptoms Scale (BNSS); Interview for the Retrospective Assessment of the Onset of Schizophrenia (IRAOS); Schedule for Affective Disorders and Schizophrenia (SADS); Negative Symptom Rating Scale (NSRS); The Positive and Negative Syndrome Scale (PANSS); Structured Interview for Prodromal Symptoms (SIPS); Scale of Prodromal Symptoms (SOPS); Global Assessment of Functioning (GAF); Scale for the Assessment of

Positive Symptoms (SAPS); Subjective Experience of Negative Symptoms (SENS); Toronto Alexithymia Scale (TAS); SUMD; Extrapyramidal Symptom Rating Scale (ESRS); Bech-Rafaelsen Melancholia Scale (BREMS); Calgary Depression Scale in Schizophrenia (CDSS); Abnormal Involuntary Movement Scale (AIMS); Operational Criteria Checklist [OPCRIT]; Multiscore Depression Inventory (MDI); Schedule for Clinical Assessment in Neuropsychiatry (SCAN); Physical Anhedonia Scale (PAS) and Social Anhedonia Scale (SAS); Thought, Language and Communication (TLC).

Table 1: Studies included in the systematic review: characteristics and conclusions (Dx = depression/depressive symptoms; Nx = negative symptoms; Px = positive symptoms)

RESULTS

2210 articles were identified. Following the removal of 892 duplicates, the titles and abstracts of the remaining 1320 articles were screened, and 75 were found to be potentially relevant. Of those 75 papers, read in full, 25 papers met the inclusion criteria and were eligible for the review. References cited in the papers were hand searched, which yielded two further eligible articles, bringing the total number of studies included to 27 (see Figure 1).

Study characteristics

Sampling

Thirteen papers reported on samples from inpatient units (16, 29, 32-34, 36-38, 41, 42, 44, 46, 47) while nine of the studies examined patients in community settings (15, 28, 30, 39, 40, 48-51). One study (22) included participants from both inpatient and outpatient units while the remaining four studies did not provide information on the source of the patient sample (31, 43, 45, 52). The study sample sizes ranged from 42 to 921 participants, with a total number of 3062.

Rating scales used

Depression scales

The majority of studies employed a single scale to assess symptoms of depression, with the most commonly used being either the Hamilton Rating Scale for

Depression (16, 22, 28, 33, 36-38, 40, 41, 52). Six studies used the Calgary Depression Scale for Schizophrenia (CDSS) (15, 42, 45, 48, 49, 51), and Five studies used the Beck Depression Inventory (22, 29, 30, 40).

Negative symptom scales

The majority of studies used either Scale for the Assessment of Negative Symptoms (SANS) (8) or the negative subscale of the Positive and Negative Syndrome Scale (PANSS) (53) to assess negative symptoms; (15, 16, 22, 28-31, 34, 36-45, 48, 49, 52). Five studies (31, 33, 39, 41, 51) used the negative subscale of the Brief Psychiatric Rating Scale (BPRS) (54). Romney et al. (22) rated anhedonia separately using Physical Anhedonia Scale (PAS) (55) and Social Anhedonia Scale (SAS) (56).

Study design and analysis

The majority of studies employed a cross-sectional design (22, 28-31, 34, 36, 39, 40, 42, 45-51). One study adopted a prospective design (16). One study employed a combined prospective and retrospective study design (15) and four studies implemented a prospective, longitudinal study design (32, 37-39). One study reported on a cross-sectional and longitudinal arm (44). An experimental design was used by two studies included in the review; Oosthuizen et al. (43) carried out an open-labelled trial and Tapp et al. (41) conducted a double-blind experiment. Newcomer et al. (33) used a retrospectively-drawn sample. In two studies (22, 50), a factor analysis was included as part of the data analysis.

Medication

Five of the 27 studies reviewed recorded the use of antidepressants, with the prevalence of antidepressant use ranging from 3 to 14% (16, 42, 43, 50, 57). Fourteen reported antipsychotic use (15, 16, 22, 32, 37-39, 41-43, 48-50, 52). Majadas et al. (49) excluded patients who were taking antidepressant medication, while Newcomer et al. (33) sampled patients who were medication naïve. Tharyan et al. (52) sampled both medicated and unmedicated patients.

Prevalence and reporting of negative symptoms and depression

The prevalence of depression in the studies reviewed ranged from 30% to 80%, depending on the criteria for the presence of depression (46, 52) or depressive symptoms (15, 16, 39, 41, 43, 45, 47, 49) that were used.

Factor analysis was reported by 2 studies, which described a depression domain independent from negative symptoms and positive symptoms (22, 50). Symptoms such as low mood, pessimism, suicidal ideation and impaired tolerance to stress were considered depressive features (31, 34). The negative symptom domain included alogia, poor attention and concentration, blunted affect and social withdrawal (28). Anhedonia, emotional blunting, anergia, amotivation, asociality and avolition occurred in both the negative and depressive domains (22, 28, 36).

Results from all of the studies reviewed were tabulated into symptoms that were reported as distinct depressive features, symptoms that were distinct negative symptoms and symptoms that overlapped between the two symptom domains (see Table 2).

Symptom	Depressive symptoms	Depressive and negative symptoms	Negative symptoms
Anhedonia		X	
Emotional blunting		X	
Anergia		X	
Amotivation		X	
Asociality		X	
Avolition		X	
Low mood	X		
Pessimism	X		
Suicidal ideation	X		
Observed sadness			X
Alogia			X
Poor attention and concentration			X
Blunted affect			X
Social withdrawal			X

Table 2: Association of symptoms within the depressive and negative symptoms domains

DISCUSSION

The findings of the studies reviewed suggest whilst considerable heterogeneity is present, some depressive features such as low mood, suicidal ideation, pessimism are distinct from a negative symptom domain characterised by alogia and blunted affect in schizophrenia. For example Liemburg et al. (10) and Messinger et al. (9) found that while depressed mood and suicidal intent reflect a depressive domain, blunted affect and alogia belong to the 'expressive deficit' negative symptom domain. Symptoms such as avolition, anergia and amotivation, considered to constitute 'social amotivation', appear to occur in both the depressive and negative domains. The findings presented are consistent with those of Whiteford et al. (28), who emphasised that while symptoms such as alogia and poor attention were distinctly negative symptoms, loss of energy and anhedonia were present in both the depressive and negative domains. Observed sadness together with inability to feel was reported as a negative symptom by

Kibel et al. in (1993) (34) as distinguished from subjective sadness. However, this was not replicated by other studies. One explanation for this finding is that there can be a misattribution of blunted affect or lack of facial expression as observed sadness.

Sax et al. (36), found the co-occurrence of depressive and negative symptoms to be confined to poor motivation, anhedonia and social withdrawal, but this may be artefactual; specifically the product of similarly worded items on different rating scales. The findings relating to whether anhedonia should be considered as part of the negative symptom or depressive symptom domains are inconsistent, and our results suggest anhedonia occurs in both. Evidence from factor analysis studies suggests that anhedonia may be more closely aligned with depression rather than schizophrenia (22, 45). Alternatively, it has been considered as a negative symptom of schizophrenia because of its close relationship with blunted affect, emotional blunting and social withdrawal (22).

The inconsistency of classification of anhedonia may partly reflect that anhedonia may be a feature of negative and depressive domains in schizophrenia in different forms, differentiated by distinguishing between anticipatory and consummatory anhedonia. Thus, anhedonia as part of depression may reflect a loss of interest in previously rewarding or enjoyable activity because of the inability to experience pleasure. However, individuals with schizophrenia may experience normal levels of pleasure when engaging in enjoyable activities (consummatory pleasure) but lack the ability to experience pleasure for future activities (anticipatory pleasure), and therefore have an anticipatory anhedonia but not a consummatory anhedonia (58). These may reflect differing underlying processes; abnormal psychological and dysfunctional behavioural processes that are responsible for differing manifestations of

anhedonia (59). However, when Li et al. (60) observed people with moderate depressive disorder and individuals with schizophrenia, they found anticipatory and consummatory anhedonia were present in both conditions. Furthermore, Buck et al. (61) observed strong correlations between scores of consummatory and anticipatory anhedonia in schizophrenia, suggesting that the explanatory value of this distinction regarding anhedonia as a negative or depressive symptom may be limited (61). However, the notion that anhedonia as a negative symptom has a different pathophysiology from its presentation as a depressive symptom is speculative and further research is needed to address this. Furthermore, the findings prompting such a notion may simply reflect a limitation in the scales used to assess the change of hedonic experiences in patients with schizophrenia.

A dimensional model within domains

If we consider negative symptoms as being formed of a diminished-expression domain and avolition-amotivation sub-domain (9), the presented findings suggest that the relationship is primarily between depression and avolition-amotivation phenomena. The relationship between depressive and negative symptoms may be represented in a dimensional model (see figure 2), with symptoms denoting general, attenuated non-specific symptoms; those that span both depressive and negative symptoms (such as anergia and poverty in speech) and those that represent specific symptoms of depression (such as consummatory anhedonia, hopelessness) and negative symptoms (such as anticipatory anhedonia, blunted affect). Levels within a dimensional hierarchy have often been implied in a positive domain e.g. social anxiety/subtle self-referential

thinking building to brief attenuated symptoms followed by frank delusional beliefs and hallucinations (see Mishara et al. (62).

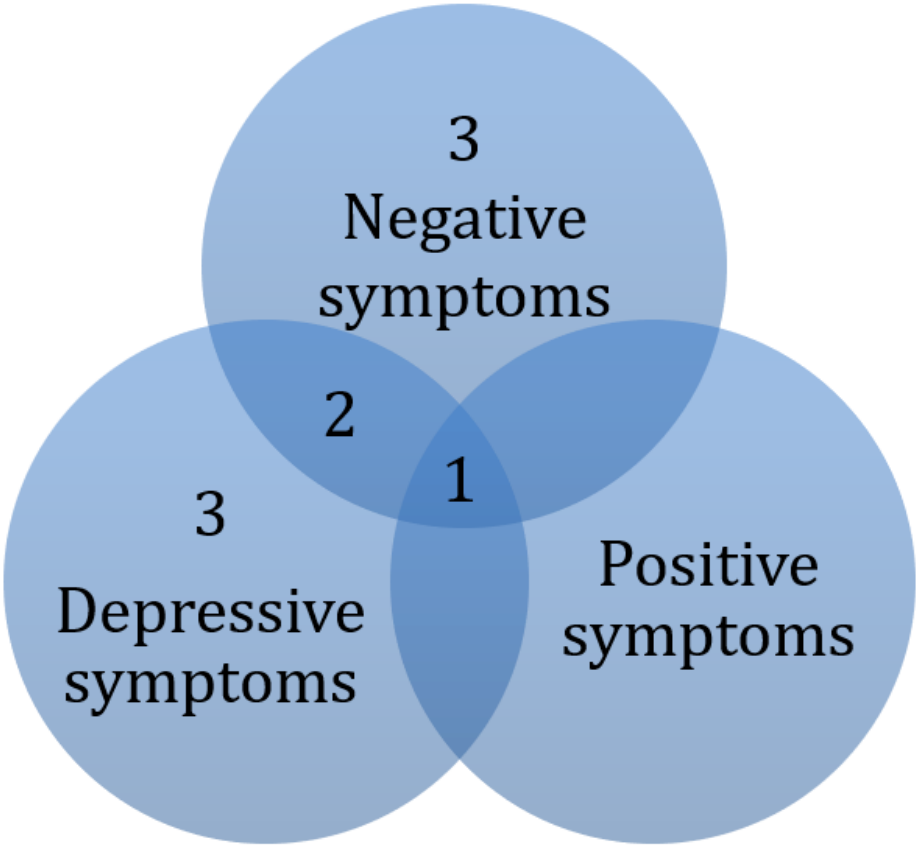

Figure 2. Dimensional model of negative, depressive and positive symptoms in schizophrenia. 1= General, attenuated non-specific symptoms; 2. Symptoms that span both depressive and negative symptoms; and 3. Symptoms specific to the depressive or negative symptoms domains

In our model, symptoms that form the expressive deficits sub-domain appear to be specific to negative symptoms, and are represented by '3' in the negative symptom domain of our dimensional model. Symptoms such as low mood, suicidal ideation and pessimism are considered core features of depression and are denoted by '3' in the depression domain. Symptoms that form the avolition-amotivation subdomain of

negative symptoms appear to consist of features that span both depressive and negative syndromes, and are represented by '2' in our dimensional model.

However only one of the studies (50) employed a scale that allows for the distinction between the two negative symptom sub-domains (the Brief Negative Symptom Scale) (63). This highlights the importance of future studies using scales able to assess the distinction between the sub-domains that form negative symptoms, such as the Clinical Assessment Interview for Negative Symptoms (CAINS: (64). This would have particular implications for studies assessing the effectiveness of domain specific interventions.

Limitations

Studies included were markedly heterogeneous; both medicated and unmedicated patients were included in the study samples as well as broad diagnostic groups including schizophrenia and first-episode psychosis. There was also a lack of consistency regarding the methods used to assess depression and negative symptoms. It can be argued that the SANS (8) provides the most comprehensive and valid coverage of negative symptom domains in schizophrenia and is highly tuned to detecting differences between positive and negative symptoms in schizophrenia, yet it was not universally used. However, the use of the SANS has its limitations not least the item assessing attention, which may be considered a manifestation of cognitive dysfunction and not form part of the negative syndrome. Nevertheless, no phenomenological measure has been developed is able to differentiate between primary and secondary negative symptoms, and the subjective experiences related to negative symptoms are

not elicited (65-67). Also, to measure depression, some studies used the HRSD (22), others used the CDSS (15) and some others used the BDI (40).

Implications

The DSM RDoC criteria and NIMH objectives recommend that research studies should focus increasingly on specific indicative symptoms to ascertain treatment effects (68, 69). Our review has suggested a putative model (see Figure 2) which could be used as a starting point for the investigation underlying biological processes and targeted treatment within a dimensional psychosis model (70-72),. Being able to clinically distinguish between depressive and negative symptoms in schizophrenia would not only allow for early, targeted treatment, but may also provide some indication of a patient's symptom burden and possibly have implications for prognosis, which can then be used to help inform a tailored treatment plan. Discriminating between anticipatory and consummatory anhedonia may prove to be a useful distinction in relation to association with either the depressive or negative domain which would suggest that the two domains within anhedonia (consummatory and anticipatory) may be products of differing aetiology.

Distinguishing between these two domains may provide clinical benefit through targeted therapy, which can be directed at either anticipatory or consummatory anhedonia and has been shown to be effective when applying psychological therapy (73). To date, there have been relatively few studies assessing the use of antidepressants to treat depression in schizophrenia and those that have been reported yielded mixed results, possibly the result of poor understanding of the core symptoms

of depression therein (74-78) Furthermore, to understand the relationship between depression and negative symptoms in schizophrenia, highly sensitive measures and thorough longitudinal studies, which chart symptom development and course, are required.

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Supplementary table 1

Search strategy for systematic review

	Database(s)	Search Term
1	Medline	exp SCHIZOPHRENIA/ OR SCHIZOPHRENIA, CATATONIC/ OR SCHIZOPHRENIA, CHILDHOOD/ OR SCHIZOPHRENIA, DISORGANIZED/ OR SCHIZOPHRENIA, PARANOID/
2	Medline	PSYCHOTIC DISORDERS/
3	Medline	(schizophren* OR psychosis OR psychoses OR FEP).ti
4	Medline	*(1 OR 2 OR 3)*
5	Medline	exp DEPRESSION/
6	Medline	(depres*).ti
7	Medline	DEPRESSIVE DISORDER/
8	Medline	DYSTHYMIC DISORDER/ OR DEPRESSIVE DISORDER, MAJOR/
9	Medline	*(5 OR 6 OR 7 OR 8)*
10	Medline	ANHEDONIA/
11	Medline	APATHY/
12	Medline	(alogia OR "affective flattening" OR "blunted affect" OR Anhedonia OR asociality OR avolition OR apathy).ti,ab
13	Medline	("social withdrawal" OR (loss ADJ1 motivat*) OR (loss ADJ1 interest) OR (lack ADJ1 motivat*) OR (lack ADJ1 interest)).ti,ab
14	Medline	("NEGATIVE SYMPTOM*").ti,ab
15	Medline	*(10 OR 11 OR 12 OR 13 OR 14)*
16	Medline	*(4 AND 9 AND 15)*
17	Medline	*16 [DT 2014-2017] [Languages English]*
18	PsycINFO	exp SCHIZOPHRENIA/
19	PsycINFO	PSYCHOSIS/
20	PsycINFO	(schizophren* OR psychosis OR psychoses OR FEP).ti
21	PsycINFO	*(18 OR 19 OR 20)*
22	PsycINFO	MAJOR DEPRESSION/ OR RECURRENT DEPRESSION/ OR TREATMENT RESISTANT DEPRESSION/
23	PsycINFO	DYSTHYMIC DISORDER/
24	PsycINFO	(depres*).ti

25	PsycINFO	*(22 OR 23 OR 24)*
26	PsycINFO	POSITIVE AND NEGATIVE SYMPTOMS/
27	PsycINFO	ANHEDONIA/
28	PsycINFO	APATHY/
29	PsycINFO	(alogia OR "affective flattening" OR "blunted affect" OR Anhedonia OR asociality OR avolition OR apathy).ti,ab
30	PsycINFO	("social withdrawal" OR (loss ADJ1 motivat*) OR (loss ADJ1 interest) OR (lack ADJ1 motivat*) OR (lack ADJ1 interest)).ti,ab
31	PsycINFO	("NEGATIVE SYMPTOM*").ti,ab
32	PsycINFO	*(26 OR 27 OR 28 OR 29 OR 30 OR 31)*
33	PsycINFO	*(21 AND 25 AND 32)*
34	PsycINFO	*33 [DT 2014-2017] [Languages English]*
35	EMBASE	*SCHIZOPHRENIA/ OR *PARANOID SCHIZOPHRENIA/ OR *PSYCHOSIS/
36	EMBASE	(schizophren* OR psychosis OR psychoses OR FEP).ti
37	EMBASE	*(35 OR 36)*
38	EMBASE	*DEPRESSION/ OR *MAJOR DEPRESSION/
39	EMBASE	*DYSTHYMIA/
40	EMBASE	(depres*).ti
41	EMBASE	*(38 OR 39 OR 40)*
42	EMBASE	*BLUNTED AFFECT/ OR *ANHEDONIA/ OR *APATHY/ OR *NEGATIVE SYNDROME/
43	EMBASE	("negative symptom*").ti,ab
44	EMBASE	(alogia OR "affective flattening" OR "blunted affect" OR Anhedonia OR asociality OR avolition OR apathy).ti,ab
45	EMBASE	("social withdrawal" OR (loss ADJ1 motivat*) OR (loss ADJ1 interest) OR (lack ADJ1 motivat*) OR (lack ADJ1 interest)).ti,ab
46	EMBASE	*(42 OR 43 OR 44 OR 45)*
47	EMBASE	*(37 AND 41 AND 46)*
48	EMBASE	*47 [DT 2014-2017] [Languages English]*
49	Medline	"MOOD DISORDERS"/
50	Medline	("mood disorder*").ti

☐	51	Medline	*(49 OR 50)*
☐	52	Medline	*(4 AND 15 AND 51)*
☐	53	Medline	*(9 OR 51)*
☐	54	Medline	*(4 AND 15 AND 53)*
☐	55	Medline	*54 [DT 2017-2018]*
☐	56	PsycINFO	"AFFECTIVE DISORDERS"/
☐	57	PsycINFO	("mood disorder*").ti
☐	58	PsycINFO	*(56 OR 57)*
☐	59	PsycINFO	*(21 AND 32 AND 58)*
☐	60	PsycINFO	*(25 OR 59)*
☐	61	PsycINFO	*(21 AND 32 AND 60)*
☐	62	PsycINFO	*61 [DT 2017-2018]*
☐	63	EMBASE	*"MOOD DISORDER"/
☐	64	EMBASE	("mood disorder*").ti
☐	65	EMBASE	*(63 OR 64)*
☐	66	EMBASE	*(37 AND 46 AND 65)*
☐	67	EMBASE	*(41 OR 65)*
☐	68	EMBASE	*(37 AND 46 AND 67)*
☐	69	EMBASE	*68 [DT 2017-2018]*

☐	86	EMBASE	*SCHIZOAFFECTIVE PSYCHOSIS/
☐	87	EMBASE	81 AND 86 [Limit to: English Language]
☐	88	EMBASE	*AFFECTIVE PSYCHOSIS/
☐	89	EMBASE	86 OR 88
☐	90	EMBASE	81 AND 89 [Limit to: English Language]
☐	91	PsycINFO	SCHIZOAFFECTIVE DISORDER/
☐	92	PsycINFO	55 AND 91 [Limit to: English Language]
☐	93	MEDLINE	SCHIZOAFFECTIVE DISORDER/
☐	95	MEDLINE	AFFECTIVE DISORDERS, PSYCHOTIC/
☐	96	MEDLINE	93 OR 95
☐	97	MEDLINE	23 AND 96 [Limit to: English Language]